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RESEARCH

Hyperchloraemia: ready for the big time?

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Chloride is in many ways the forgotten electrolyte. Recent evidence suggests that hyperchloraemia results in metabolic acidosis, and is associated with renal dysfunction, increased mortality, coagulation disturbances, splanchnic ischaemia, and a proinflammatory state. The renal effects and the increased mortality are the best established and most concerning of these associations. The choice of intravenous fluids significantly influences the development of hyperchloraemia. Further studies are required to confirm or refute these associations. In the interim high-chloride fluids, most commonly 0.9% saline, should be avoided as resuscitation fluids.

Keywords: acute kidney injury, chloride, critical care, hyperchloraemia, mortality, perioperative

Introduction

Chloride is a Cinderella electrolyte and is often viewed as a passive companion to sodium. A PubMed search (February 7, 2015) revealed 236 results for 'hyperchloraemia' and 3071 for 'hypernatraemia'. Emerging evidence suggests, however, that chloride is a powerful, biologically active electrolyte in its own right and that hyperchloraemia is associated with adverse outcomes.

Basic science

Chloride is the major strong anion in plasma, accounting for two-thirds of all negative charges in plasma, and one-third of plasma tonicity[1,2]. These contributions are even greater in interstitial fluid as there is minimal anionic protein in this compartment. Normal plasma chloride is in the range of 97–107 mmol/l, with low intracellular concentrations of approximately 10 mmol/l[1,2]. Daily chloride intake is approximately 150 mmol, equivalent to a litre of 0.9% saline a day[1].

Although beyond the scope of this review chloride channels are extensively distributed and are important for a range of biological effects from fluid secretion to cell volume regulation and neurological functioning[1,2].

Incidence

Hyperchloraemia is common in the perioperative and critical care setting. A recent large cohort study in unselected postoperative patients reported an incidence of acute postoperative hyperchloraemia of 22%[3]. This may rise to as high as 57.7% in selected surgical intensive care populations[4]. Severe hyperchloraemia was noted to occur in 6.2% of patients in a multidisciplinary intensive care unit (ICU)[5].

Aetiology

As Table 1 shows, hyperchloraemia has multiple potential causes and is often multifactorial.

The question of whether our choice of intravenous fluid really influences serum chloride is key to further discussions on this topic and warrants further exploration.

In a study comparing the effects of just two litres of 0.9% saline versus Plasma-Lyte on healthy volunteers, a rapid rise in serum chloride was seen in the saline group and chloride levels remained significantly higher in the saline group than the Plasma-Lyte group for the four hours of the study[6].

A Cochrane review of perioperative fluid therapy showed a significantly higher plasma chloride in patients receiving 0.9% saline versus those receiving a balanced salt solution (114.0 vs. 106.9 mmol/l $p = 0.0001$)[7]. Yunos demonstrated significantly higher mean chloride levels in a saline-based fluid group versus a balanced salt solution group[5]. A recent study in trauma patients resuscitated with either 0.9% saline or a balanced salt solution showed a significantly higher serum chloride in the saline group: 111 vs. 104; difference: –7 (95% CI: –10 to –3)[8]. It is clear, then, that our choice of fluid influences plasma chloride levels; in particular the use of 0.9% saline solutions increases plasma chloride and puts the patient at risk of hyperchloraemia.

Does hyperchloraemia matter?

While it is now clear that hyperchloraemia is common and the incidence is influenced by our choice of intravenous fluid, does this hyperchloraemia have any adverse effects? The rest of the review will explore this question in further detail.

Metabolic acidosis

Hyperchloraemia has been associated with a normal anion gap metabolic acidosis. Although beyond the scope of this review, this is elegantly explained conceptually by Stewart's hypothesis, whereby a relative increase in serum chloride reduces strong ion difference (SID), and to maintain electroneutrality the dissociation of water produces hydrogen ions. In this theory it is important to note that chloride is the driver of the acidosis and not a passive participant in exchange for bicarbonate as seen in more traditional explanations.

While theoretically attractive it must be questioned whether high-chloride fluids and hyperchloraemia lead to an acidosis clinically. Mathematical modelling, laboratory data and animal studies have shown that it is the relationship of the SID of the infused fluid to the patient's bicarbonate or SID that determines the effect of fluid infusion on the subject's acid-base status[9,10]. As a result of the high chloride content, the SID of 0.9% saline is less than that of plasma bicarbonate/SID and thus leads to an acidosis. A fluid with an SID equal to or higher than the bicarbonate/SID of plasma (e.g. Ringer's lactate) leads, respectively, to no change in pH or an alkalosis.

Table 1: Aetiology of hyperchloraemia

Cause	Examples	
Chloride infusion	Administration of chloride-rich fluids	e.g. 0.9% sodium chloride
	Total parenteral nutrition	
Pure water loss	Skin	Fever
		Hypermetabolic states
	Renal	Diuretics
		Central diabetes insipidus
		Nephrogenic diabetes insipidus
Water loss in excess of chloride loss	Extrarenal	Diarrhoea
		Burns
	Renal	Osmotic diuresis
		Post-obstructive diuresis
		Intrinsic renal disease
Definite or relative increase in tubular chloride reabsorption	Renal tubular acidosis	
	Recovery of diabetic ketoacidosis	
	Early renal failure	
	Acetazolamide	
	Ureteral diversion procedures	
	Post-hypocapnia	

Note: Modified from Yunos et al.[1]

In terms of human clinical data, Scheingraber compared fluid therapy in two groups of patients undergoing major gynaecological surgery[11]. One group received isotonic saline at 30 ml/kg/h and the other received Ringer's lactate at the same rate. The saline group rapidly developed hyperchloraemia and an acidosis, which was not seen in the Ringer's group. At two hours the mean base excess had dropped from –0.4 to –6.7 mmol/l in the saline group, the pH from 7.41 to 7.28 and the chloride had risen from 104 to 115 mmol/l. These are extreme fluid volumes for elective surgery but they graphically illustrate the point. Waters et al. demonstrated that hyperchloraemia was significantly correlated with an increase in base deficit intraoperatively[12]. In the Yunos study alluded to earlier the investigators conducted a prospective before and after study where they collected baseline data in their ICU for six months and then phased out the use of saline-based fluids[5]. They then repeated their data collection for six months and compared the two sets of data. Saline use fell from 2411 l in the control group to 52 l in the intervention group and balanced salt solution use increased from 469 l to 3205 l. This change was associated with a significant reduction in severe hyperchloraemia and a concomitant reduction in severe metabolic acidosis and acidaemia. A study in septic paediatric patients further showed that there is a linear relationship between chloride load and base deficit — in other words there is a clear dose–response relationship between chloride-containing fluids and acidosis[13]. In the trauma study by Young et al. the base deficit normalised within 6 h in the balanced salt solution group and remained in the normal range for the duration of the study but remained abnormal (elevated) throughout the 24-h study period in the 0.9% saline group[8].

It is thus clear that hyperchloraemia is associated with a metabolic acidosis and acidotic patients tend to have poorer clinical outcomes[14–16]. It is, however, unclear whether the acidosis per se leads to adverse clinical outcomes or whether it is the underlying physiological derangement that determines the clinical consequences. As an example, one of the commonly quoted adverse effects of acidosis is reduced myocardial contractility[17,18]. It appears that the type of acidosis may determine the degree of myocardial depression, with ketoacidotic patients even showing normal or increased myocardial contractility in some studies[19–21]. In terms of mortality it has been shown that lactate and base deficit both predict mortality but there may be poor correlation between these variables, suggesting that the effect of the anion and the acidosis may be separate[15,22]. In addition Gunnerson et al. demonstrated a differential mortality according to type of acidosis in a retrospective cohort analysis of intensive care patients. The inpatient mortality rate was 56% for lactic acidosis, 39% for strong ion gap acidosis and 29% for hyperchloraemic acidosis ($p < 0.001$), with the baseline mortality rate of the entire cohort being 14%[14]. The exact clinical effect of the acidosis associated with hyperchloraemia thus remains unclear, but hyperchloraemic acidosis can still confound clinical management, e.g. in a patient with diabetic ketoacidosis (DKA), receiving 0.9% saline, a worsening acidaemia may be due to inadequate fluid volume or hyperchloraemia, the two scenarios requiring conflicting fluid strategies. In addition emerging evidence suggests that hyperchloraemia itself may be problematic, beyond a simple acid-base effect. This will be explored further below.

Renal dysfunction

As long ago as 1983, it was shown in a canine model that hyperchloraemia induces renal vasoconstriction and reduces glomerular filtration rate (GFR). This vasoconstrictive effect was specific to the renal vasculature[23]. Chowdhury showed in human volunteers that two litres of 0.9% saline reduced renal artery blood flow and renal cortical perfusion — an effect not seen with Plasma-Lyte[6].

Chowdhury also recently reported that a starch in a balanced salt solution increased renal cortical perfusion versus a saline-based starch[24]. In another volunteer study, subjects given Hartmann's solution showed an earlier time to first micturition and a greater urine output over six hours than patients given 0.9% saline. This greater diuresis has been ascribed to the lower osmolality of Hartmann's solution causing reduced vasopressin secretion. This is unlikely to be the sole explanation though, as the Hartmann's group also had a greater sodium excretion which suggests a primarily renal effect — possibly due to the difference in chloride load[25]. In a follow-up paper to Yunos's initial study evaluating the biochemical effects of restricting chloride-rich fluids the investiga-

tors evaluated the effect of this change in fluid therapy on clinical outcomes. They reported a significant reduction in acute kidney injury (AKI) and renal replacement therapy (RRT) in the chloride-restrictive group[26]. While these are only observational data this is amongst the first evidence that changing our choice of fluid and restricting chloride-containing fluids can change clinical outcomes. A recently published observational study in liver transplant recipients identified the use of large volumes of chloride-rich fluids as an independent predictor of AKI[27]. In contrast, the Cochrane review mentioned above suggested no difference in renal dysfunction and RRT between the chloride-rich and balanced salt groups[7]. It evaluated randomised studies of buffered vs. non-buffered fluids for perioperative fluid resuscitation up to May 2011, and included data from 14 publications. Of these only three (n = 207) reported on 'renal insufficiency requiring support', seven (n = 399) reported intraoperative urine output, and three (n = 222) reported postoperative creatinine clearance. In addition five studies reported various creatinine-based indices but there were only two studies per category (n = 113–151). This review thus included small numbers and did not specifically evaluate the development of AKI using current standard definitions; therefore the results regarding renal dysfunction should be viewed with caution.

Splanchnic circulation

Concerns have also been raised over the effects of hyperchloraemia on the splanchnic circulation. A volunteer crossover study raised initial concerns with an increased incidence of abdominal discomfort in the 0.9% saline versus the Ringer's lactate group[28]. A subsequent study on elderly surgical patients demonstrated a higher gastric tonometry CO_2 gap in the saline versus the balanced-salt group[29]. This suggests reduced gastric perfusion in the saline group. Interestingly abdominal symptoms are key features of ammonium chloride poisoning, suggesting a link between chloride and the above findings. While current evidence is limited, gut hypoperfusion and bacterial translocation may predispose patients to septic complications and this is thus an area of concern and should be a focus for future research[30–33].

Sepsis

There are also concerns about the effects of hyperchloraemia in sepsis, although the evidence is limited to laboratory data and animal studies. Studies in rat models of septic shock have shown a worse acid-base profile in animals receiving 0.9% saline as opposed to lower chloride solutions[34]. The same group also demonstrated a significant correlation between an increase in chloride levels and hypotension in their rat model[35]. Investigating the cause of these findings the researchers found that hyperchloraemic acidosis induced increased NF-kB DNA binding, increased nitric oxide release, and increased interleukin (IL) 6: IL 10 ratios in cell culture, suggesting a proinflammatory effect at the cellular level[36]. Further research on this in a rat model confirmed that hyperchloraemic acidosis was associated with an increased cytokine release as compared with controls resuscitated with Ringer's lactate[37]. While this animal research suggests that hyperchloraemia has adverse haemodynamic and inflammatory effects in sepsis we simply do not have human data to confirm or refute these findings.

Haemostasis and haemorrhage

The effect of hyperchloraemic fluids on haemostasis and haemorrhage has also been investigated.

In a series of studies by Roche and James, saline-based starches appeared to impair coagulation to a greater degree than equivalent balanced salt solution starches and Ringer's lactate[38,39]. This appears not to be related to differences in calcium content between fluids, which leaves us to hypothesise about the role of primary chloride or secondary acid-base differences being the driving factor[40]. In terms of clinical studies, Martin showed that in patients undergoing major surgery those who received a starch in saline had a hypocoagulable thromboelastograph (TEG) compared with those who received a starch in a balanced salt solution, whereas those who received Ringer's lactate tended to develop a hypercoagulable state[41]. In a trial involving patients undergoing major surgery, those who received a saline-based colloid had significant TEG abnormalities and increased blood loss compared with those receiving a balanced salt-solution colloid[42]. In a study involving patients undergoing abdominal aortic aneurysm repair, those who received 0.9% saline had greater blood loss and received more blood products than those who received Ringer's lactate[43]. In contrast to the above, there was no difference in the international normalised ratio and activated partial thromboplastin time in trauma patients resuscitated with either 0.9% saline or Plasma-Lyte A[8]. This study did not, however, use the TEG. The data are thus by no means conclusive but do raise a concern regarding the potential for chloride-rich fluids to impair coagulation. Further clinical studies, either removing the confounder of colloid-based fluids or using modern colloids, and using the TEG as a standardised assessment of coagulation, are warranted.

Mortality

While the basic science, animal studies and human surrogate outcome/organ dysfunction studies have raised concerns about hyperchloraemia, is there any evidence of an effect on mortality in human studies?

The Cochrane review mentioned previously included only three trials that reported mortality outcomes and showed no difference in mortality in perioperative patients whether they received saline or a balanced salt solution[7].

Yunos's study, which highlighted the effect of high-chloride fluids on AKI and RRT, also did not demonstrate a mortality difference[26].

In contrast to this is a thought-provoking study from Brazil[44]. The authors prospectively evaluated major surgical patients who required postoperative intensive care. They recruited 393 patients and analysed their postoperative chloride levels. Instead of using standard definitions of hyperchloraemia they constructed a receiver operating characteristic curve of chloride levels and hospital mortality. This showed an optimal cut-off point of 114 mmol/l and a reasonable area under the curve (AUC) for predicting death of 0.76. Using this cut-off, 31.7% of the patients were hyperchloraemic. Comparing mortality between those above and below the cut-off they found a significantly higher mortality in the hyperchloraemic patients (19.3 vs. 7.4%; p = 0.001). These patients, however, had significantly longer surgery and received more intraoperative saline. Based on this it cannot be said whether the hyperchloraemia is causative or merely a marker of increased risk but it does raise serious concerns regarding the potential risks of iatrogenic hyperchloraemia.

In another Brazilian study, Boniatti evaluated a number of acid-base and biochemical variables as predictors of mortality in ICU[4]. While many showed an association on univariate analysis, only chloride and albumin remained significant on multivariate analysis and improved the predictive ability of a multiple logistic regression model consisting of SOFA score and age, increasing the AUC from 0.72 to 0.8. Again we have hyperchloraemia as a significant marker of poor outcome but no clarity on cause and effect.

Most recently, McCluskey reported that acute postoperative hyperchloraemia was associated with an increased risk of 30-day mortality (3.4 vs. 1.3%; $p < 0.01$). This was a large retrospective cohort study involving over 22 000 patients who underwent inpatient non-cardiac, non-transplant surgery. The study also included propensity matching of hyperchloraemic and non-hyperchloraemic patients. The excess mortality in hyperchloraemic patients was still seen in this propensity-matched cohort (3.0 vs. 1.9%; $p < 0.01$). Hyperchloraemia was found to be an independent predictor of mortality in multiple logistic regression analysis (odds ratio = 2.049; 95% CI 1.619–2.592; $p < 0.01$).

While not conclusive, this association with mortality raises serious concerns and needs to be explored further.

Conclusion

Hyperchloraemia leads to the development of metabolic acidosis and is associated with adverse renal effects and increased mortality, amongst other adverse effects. It is also apparent that our choice of intravenous fluids influences the development of hyperchloraemia. From a research perspective we need to explore further the association between hyperchloraemia and adverse outcomes in different populations and attempt to elucidate whether the hyperchloraemia is indeed contributing to any associated adverse outcomes in the clinical setting. We also need to explore whether preventing or treating hyperchloraemia results in improved clinical outcomes. In the interim it is prudent to avoid the use of 0.9% saline as a resuscitation fluid, and to avoid often unconsidered sources of chloride where possible, e.g. the use of colloids in 0.9% saline and the use of 0.9% saline as a diluent for large-volume medication infusions.

Conflict of interest – The author declares that he has no financial or personal relationship(s) which may have inappropriately influenced him in writing this paper.

References

1. Yunos NM, Bellomo R, Story D, et al. Bench-to-bedside review: chloride in critical illness. Crit Care (London, England). 2010;14(4):226. PubMed PMID: 20663180. Pubmed Central PMCID: PMC2945073. Epub 2010/07/29. eng.
2. Berend K, van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes? Eur J Intern Med. 2012 Apr;23(3):203–11.
3. McCluskey SA, Karkouti K, Wijeysundera D, et al. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg. 2013 Aug;117(2):412–21. PubMed PMID: 23757473. Epub 2013/06/13. eng.
4. Boniatti MM, Cardoso PR, Castilho RK, et al. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. J Critic Care. 2011 Apr;26(2):175–9.
5. Yunos NM, Kim IB, Bellomo R, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. Crit Care Med. 2011 Nov;39(11):2419–24.
6. Chowdhury AH, Cox EF, Francis ST, et al. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012 Jul;256(1):18–24. PubMed PMID: 22580944.
7. Burdett E, Dushianthan A, Bennett-Guerrero E, et al. Perioperative buffered versus non-buffered fluid administration for surgery in adults. Cochrane Database Syst Rev. 2012;12:CD004089. PubMed PMID: 23235602. Epub 2012/12/14. eng.
8. Young JB, Utter GH, Schermer CR, et al. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. Ann Surg. 2014 Feb;259(2):255–62. PubMed PMID: 23732264. Epub 2013/06/05. eng.
9. Carlesso E, Maiocchi G, Tallarini F, et al. The rule regulating pH changes during crystalloid infusion. Intensive Care Med. 2011 Mar;37(3):461–8. PubMed PMID: 21152898. Epub 2010/12/15. eng.
10. Morgan T, Venkatesh B, Beindorf A, et al. Acid-base and bio-energetics during balanced versus unbalanced normovolaemic haemodilution. Anaesth Intensive Care. 2007;35(2):173–9.
11. Scheingraber S, Rehm M, Sehmisch C, et al. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology. 1999 May;90(5):1265–70. PubMed PMID: 10319771. Epub 1999/05/13. eng.
12. Waters JH, Miller LR, Clack S, et al. Cause of metabolic acidosis in prolonged surgery. Crit Care Med. 1999 Oct;27(10):2142–6. PubMed PMID: 10548196. Epub 1999/11/05. eng.
13. O'Dell E, Tibby SM, Durward A, et al. Hyperchloremia is the dominant cause of metabolic acidosis in the postresuscitation phase of pediatric meningococcal sepsis. Crit Care Med. 2007 Oct;35(10):2390–4. PubMed PMID: 17717489. Epub 2007/08/25. eng.
14. Gunnerson KJ, Saul M, He S, et al. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care (London, England). 2006 Feb;10(1):R22. PubMed PMID: 16507145. Pubmed Central PMCID: PMC1550830. Epub 2006/03/02. eng.
15. Martin MJ, FitzSullivan E, Salim A, et al. Discordance between lactate and base deficit in the surgical intensive care unit: which one do you trust? Am J Surg. 2006 May;191(5):625–30. PubMed PMID: 16647349. Epub 2006/05/02. eng.
16. Smith I, Kumar P, Molloy S, et al. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med. 2001 Jan;27(1):74–83.
17. Teplinsky K, O'Toole M, Olman M, et al. Effect of lactic acidosis on canine hemodynamics and left ventricular function. Am J Physiol. 1990 Apr;258(4 Pt 2):H1193–9. PubMed PMID: 2331007. Epub 1990/04/01. eng.
18. Cingolani HE, Faulkner SL, Mattiazzi AR, et al. Depression of human myocardial contractility with "respiratory" and "metabolic" acidosis. Surgery. 1975 Mar;77(3):427–32. PubMed PMID: 1124498. Epub 1975/03/11. eng.
19. Berger DS, Fellner SK, Robinson KA, et al. Disparate effects of three types of extracellular acidosis on left ventricular function. Am J Physiol. 1999 Feb;276(2 Pt 2):H582–94. PubMed PMID: 9950860. Epub 1999/02/10. eng.
20. Maury E, Vassal T, Offenstadt G. Cardiac contractility during severe ketoacidosis. N Eng0l J Med. 1999 Dec 16;341(25):1938. PubMed PMID: 10610482. Epub 1999/12/28. eng.
21. George AK, Shih A, Regan TJ. Effect of acute ketoacidosis on the myocardium in diabetes. Am J Med Sci. 1996 Feb;311(2):61–4. PubMed PMID: 8615375. Epub 1996/02/01. eng.
22. Husain FA, Martin MJ, Mullenix PS, et al. Serum lactate and base deficit as predictors of mortality and morbidity. Am J Surg. 2003 May;185(5):485–91. PubMed PMID: 12727572. Epub 2003/05/03. eng.
23. Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest. 1983 Mar;71(3):726–35. PubMed PMID: 6826732. Pubmed Central PMCID: PMC436923. Epub 1983/03/01. eng.
24. Chowdhury AH, Cox EF, Francis ST, et al. A randomized, controlled, double-blind crossover study on the effects of 1-l infusions of 6% hydroxyethyl starch suspended in 0.9% saline (voluven) and a balanced solution (Plasma Volume Redibag) on blood volume, renal blood flow velocity, and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2014 May;259(5):881–7. PubMed PMID: 24253140. Epub 2013/11/21. eng.
25. Reid F, Lobo DN, Williams RN, et al. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (London, England: 1979). 2003 Jan;104(1):17–24. PubMed PMID: 12519083. Epub 2003/01/10. eng.
26. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012 Oct 17;308(15):1566–72. PubMed PMID: 23073953. Epub 2012/10/18. eng.
27. Nadeem A, Salahuddin N, El Hazmi A, et al. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. Crit Care (London, England). 2014 Nov 19;18(6):3634. PubMed PMID: 25407504. Pubmed Central PMCID: PMC4258383. Epub 2014/11/20. Eng.
28. Williams EL, Hildebrand KL, McCormick SA, et al. The effect of i ntravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. Anesth

Analg. 1999 May;88(5):999–1003. PubMed PMID: 10320158. Epub 1999/05/13. eng.
29. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg. 2001 Oct;93(4):811–6. PubMed PMID: 11574338. Epub 2001/09/28. eng.
30. MacFie J, Reddy BS, Gatt M, et al. Bacterial translocation studied in 927 patients over 13 years. Br J Surg. 2006 Jan;93(1):87–93. PubMed PMID: 16288452. Epub 2005/11/17. eng.
31. O'Boyle CJ, MacFie J, Mitchell CJ, et al. Microbiology of bacterial translocation in humans. Gut. 1998 Jan;42(1):29–35. PubMed PMID: 9505882. Pubmed Central PMCID: PMC1726947. Epub 1998/03/20. eng.
32. Holland J, Carey M, Hughes N, et al. Intraoperative splanchnic hypoperfusion, increased intestinal permeability, down-regulation of monocyte class II major histocompatibility complex expression, exaggerated acute phase response, and sepsis. Am J Surg. 2005 Sep;190(3):393–400. PubMed PMID: 16105525. Epub 2005/08/18. eng.
33. Ziegler TR, Smith RJ, O'Dwyer ST, et al. Increased intestinal permeability associated with infection in burn patients. Arch Surg (Chicago, Ill : 1960). 1988 Nov;123(11):1313–9. PubMed PMID: 3140766. Epub 1988/11/01. eng.
34. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. Crit Care Med. 2002 Feb;30(2):300–5. PubMed PMID: 11889298. Epub 2002/03/13. eng.
35. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. Chest. 2004 Jan;125(1):243–8. PubMed PMID: 14718447. Epub 2004/01/14. eng.
36. Kellum JA, Song M, Li J. Lactic and hydrochloric acids induce different patterns of inflammatory response in LPS-stimulated RAW 264.7 cells. Am J Physiol Regul Integr Comp Physiol. 2004 Apr;286(4):R686–92. PubMed PMID: 14695114. Epub 2003/12/26. eng.
37. Kellum JA, Song M, Almasri E. Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. Chest. 2006 Oct;130(4):962–7.
38. Roche AM, James MF, Grocott MP, et al. Coagulation effects of in vitro serial haemodilution with a balanced electrolyte hetastarch solution compared with a saline-based hetastarch solution and lactated Ringer's solution. Anaesth. 2002 Oct;57(10):950–5. PubMed PMID: 12358952. Epub 2002/10/03. eng.
39. Roche AM, James MF, Bennett-Guerrero E, et al. A head-to-head comparison of the in vitro coagulation effects of saline-based and balanced electrolyte crystalloid and colloid intravenous fluids. Anesth Analg. 2006 Apr;102(4):1274–9. PubMed PMID: 16551936. Epub 2006/03/23. eng.
40. Roche AM, James MF, Bennett-Guerrero E, et al. Calcium supplementation of saline-based colloids does not produce equivalent coagulation profiles to similarly balanced salt preparations. J Cardiothorac Vasc Anesth. 2006 Dec;20(6):807–11. PubMed PMID: 17138085. Epub 2006/12/02. eng.
41. Martin G, Bennett-Guerrero E, Wakeling H, et al. A prospective, randomized comparison of thromboelastographic coagulation profile in patients receiving lactated Ringer's solution, 6% hetastarch in a balanced-saline vehicle, or 6% hetastarch in saline during major surgery. J Cardiothorac Vasc Anesth. 2002 Aug;16(4):441–6. PubMed PMID: 12154422. Epub 2002/08/03. eng.
42. Gan TJ, Bennett-Guerrero E, Phillips-Bute B, et al. Hextend, a physiologically balanced plasma expander for large volume use in major surgery: a randomized phase III clinical trial. Hextend study group. Anesth Analg. 1999 May;88(5):992–8. PubMed PMID: 10320157. Epub 1999/05/13. eng.
43. Waters JH, Gottlieb A, Schoenwald P, et al. Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg. 2001 Oct;93(4):817–22. PubMed PMID: 11574339. Epub 2001/09/28. eng.
44. Silva Junior JM, Neves EF, Santana TC, et al. The importance of intraoperative hyperchloremia. Rev. Bras. Anestesiol. 2009 May–Jun;59(3):304–13. PubMed PMID: 19488543. Epub 2009/06/03. eng por.

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